

Commentary on: “A multi-institutional experience in pediatric high grade glioma”

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A commentary on

A multi-institutional experience in pediatric high-grade glioma

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This multi-institutional retrospective study evaluates the association of clinical, pathological, and treatment characteristics with their outcomes. Their results show total resection and receiving chemotherapy adjuvant to radiation or chemoradiation are most strongly related with improved progression-free survival (PFS) and overall survival. For higher risk incompletely resected patients, temozolomide (TMZ) use and treatment intensification with concurrent chemoradiation, adjuvant chemotherapy, and higher radiation dose were associated with improved outcomes. It is a well written and conducted paper about a remarkable challenge to neurosurgeon and pediatric oncologists. Little progress has been made in the outcome of these tumors in the last four decades. Outcome remains dismal with <20% of patients surviving (1). The degree of surgical resection is one of the most important clinical prognostic factors known in children with supratentorial high-grade gliomas (HGGs), independent of location, histology, and age as the authors show (2).

Chemotherapy was first introduced into the treatment schema for children with newly diagnosed HGG in 1970s. One the first randomized study was CCG-943 trial, in which children with newly diagnosed HGG were randomized to receive either focal radiation therapy alone to a

dose of 54 Gy or the same radiotherapy with a combination of concomitant and maintenance chemotherapy. Patients randomized to receive chemotherapy were given weekly vincristine during radiation followed by eight maintenance chemotherapy cycles consisting of prednisone, lomustine, and vincristine (PCV) each given approximately 6 weeks apart (3). This important study showed that treatment with chemotherapy prolonged the survival and event-free survival. The Children's Cancer Group (CCG) study-945 showed that children with HGG who underwent a surgical resection of 90% or greater had a PFS of $35 \pm 7\%$ as compared to a 5-year PFS of $17 \pm 4\%$ in patients who did not (4). The authors did not refer any benefit to the treatment of high-grade astrocytomas in children with eight-drugs in 1-day chemotherapy compared with CCNU, vincristine, and prednisone. Extent of tumor resection and histopathologic diagnosis were significant prognostic variables (4). The CCG-945 trial also looked at a variety of molecular and cytogenetic markers in an effort to better define prognostic variables in pediatric HGG.

Currently, the efficacy of chemotherapeutic compounds against pediatric brain tumors is unsatisfactory. Efficacy of TMZ has generally been found to be non-superior to other chemotherapeutic agents in pediatric HGG, and various studies in children have shown no benefit over conventional treatment (5). Cilen-gitide was well tolerated in pediatric HGG, yet had modest anti-tumor activity as a single agent (6). However, cilen-gitide in combination with radiation and

chemotherapy, TMZ, has shown synergistic activity (7). Phase I or II studies of small molecules that target specific pathways or proteins in the cancer cells such as gefitinib (8), imatinib (9), cloretazine (10), tipifarnib (11), erlotinib (12), and nimotuzumab (13) disclosed no efficacy, despite occasional remarks of stable disease (1). Recently, fractionated schedules of drug administration using smaller doses than the maximum tolerated dose (metronomic schedules) have been reported that might enhance the antiangiogenic activity of some chemotherapeutic agents (14). Metronomic chemotherapy shows potential advantages in pediatric brain tumors treatment, including primary effect on the host cells of the tumor microenvironment, the possibility of greater long-term efficacy and tolerability than conventional cytotoxic therapy (14).

In recent years, important advances in the comprehension of the molecular characteristics of HGG in pediatric age have been made. Initial genomic studies of pediatric HGG disclosed significant differences compared to tumors from adult patients suggesting the existence of molecularly diverse subsets within pediatric cohorts. Data about the interactions between genetic alterations and changes in DNA methylation, histone modifications, chromatin remodeling, and gene expression contribute to explain pathogenesis of malignant gliomas. Adult HGG are characterized by IDH1, PTEN, and/or EGFR aberrations; whereas pediatric HGG often harbors PDGFR amplification. PDGFR amplification or overexpression represents the most common abnormality of HGG

in pediatric patients (15). BRAF and CDKN2A mutations have been reported to characterize HGG in a subset of pediatric patients, although BRAF abnormalities are not as frequently as described in childhood low-grade glioma (15). Schwartzentruber et al. reported in a large cohort of gliomas of various grades and histologies H3F3A mutations to be prevalent in children and young adults affected by malignant gliomas (16). Mutations of genes H3F3A and HIST1H3B are epigenetic and play a role in chromatin remodeling (17). Mutations in IDH1 or IDH2 are exceptional in pediatric patients but occur in the majority of adult patients with HGG. A study of pediatric primary HGG from the Children's Oncology Group observed IDH1 mutations in 7 of 43 tumors. Remarkably, all of these IDH1 mutations occurred in children ≥ 14 years old, with none occurring in younger children. No IDH2 mutations were observed (18). IDH1 mutations at codon 132 strongly differentiate adult secondary from primary glioblastoma, with frequencies of 85% compared with 5%. Paugh et al. sequenced IDH1 exon 4, containing codon 132, from 78 pediatric HGGs and 11 pediatric low-grade gliomas, and no codon 132 mutations were detected (15).

The recent genomic groundbreaking work added tremendously to our understanding of the mutational landscape of pediatric HGG, bringing to light new, potentially targetable pathways, and promise of more effective therapies. In light of these observations, new trials and emerging data about pediatric HGG could improve the outcome of HGG in children and young adults.

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